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09/446,145	01/07/2000	HIROSHI MIYAKE	0018-1086-PC	1855

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[REDACTED] EXAMINER

PATEL, SUDHAKER B

[REDACTED] ART UNIT

[REDACTED] PAPER NUMBER

1624

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. <b>09/446,145</b>	Applicant(s) <b>HIROSHI MIYAKE et al</b>
	Examiner <b>Sudhaker Patel</b>	Art Unit <b>1624</b>



*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1)  Responsive to communication(s) filed on Mar 6, 2002

2a)  This action is FINAL.      2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle* 1035 C.D. 11; 453 O.G. 213.

#### Disposition of Claims

4)  Claim(s) 1-6 and 8 is/are pending in the applica

4a) Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from considera

5)  Claim(s) \_\_\_\_\_ is/are allowed.

6)  Claim(s) 1-6 and 8 is/are rejected.

7)  Claim(s) \_\_\_\_\_ is/are objected to.

8)  Claims \_\_\_\_\_ are subject to restriction and/or election requirem

#### Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are a)  accepted or b)  objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)  The proposed drawing correction filed on \_\_\_\_\_ is: a)  approved b)  disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)  The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13)  Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)  All b)  Some\* c)  None of:

1.  Certified copies of the priority documents have been received.

2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)  The translation of the foreign language provisional application has been received.

15)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                   | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)          | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ | 6) <input type="checkbox"/> Other: _____                                    |

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## **DETAILED ACTION**

Applicants' communication paper 10 dated 3/6/02 is acknowledged.

Applicants have canceled claims 7,9, and 10.

(1). **Election/Restriction:** The examiner finds that Applicants' arguments are not persuasive concerning the traversal, therefore, the finding is maintained. Applicants are required to cancel the non-elected subject matter in the next communication.

♦ According to 37 CFR 1.499(see MPEP 1893.03(d)), the examiner may in an Office Action require the applicants in the response to that action to elect the invention to which the claims shall be restricted, if the Examiner finds that a national stage application lacks unity of invention under 37 CFR 1.475.

♦ The pertinent aspects of Rule 37 1.475 are:

(b). An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combination of categories:

(3). A product, a process specially adapted for the manufacture of the said product, and a use of the said product;

(5). A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process;

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(c). If an application contains claims to more or less than one of the combinations of categories of invention set forth in the paragraph (b) of this section, unity of invention might not be present.

The claims are drawn to both (b)(3) and (b)(5), i.e. A product, a process specially adapted for the manufacture of the said product, an apparatus or means specifically designed for carrying out the said process, and a use of the said product. The finding of a lack of unity rests on the fact that there are more than one product claimed, which according to (2)(c) the finding is permitted. Thus the Examiner's restriction requirement is not seen to be inconsistent with the unity of invention provisions of the PCT treaty.

- ♦ The guidelines for establishing lack of unity for claims which are drawn to more than one product, i.e. drawn to alternative compounds not having a corresponding technical feature, are found in MPEP 1850, wherein "Markush Practice" is defined as follows:
- ♦ The situation involving the so-called Markush practice wherein a single claim defines alternatives(chemical or non-chemical) is also governed by PCT Rule 13.2. In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature.
- ♦ When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

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(A) all alternatives have a common property or activity; and

(B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives;

or

(C)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

In paragraph (B)(1), above, the words significant structural element is shared by all of the alternatives refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art (see WO 9637489 claims 1,8; WO 9634864 see abstract and claim 1 and Example 14 on page 71; WO 9708166 see abstract and claim 1 on page 94; EP 655442 see abstract, claim 1, compounds 50-44, 50-48 in Table 1, and compounds 51-51-11 in Table 2 pages 8284). The structural element may be a single component or a combination of individual components linked together.

♦ The Examiner maintains that the requirement of (B)(1) has not been met since the structural element common to all of the alternatives, i.e. BIS-haloalkyl substituted phenyl/aryl-CO-[(YR2)(R3)substituted piperazine]-R4 are chemical equivalents and they do not constitute a portion of the compound's structure to be considered structurally distinctive and patentably distinct. The side chain claimed as novelty of the elected

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species consists of the specific substituent R4( = -Alkylene-C=C-Alkylene-1,4-oxazine) which represents one of the variables of 1,4-piperazine ring.

♦ Applicants elected(see paper No.6 dated 6/19/00) with traverse invention of Group I claims(in part) 1-6,8, drawn to compounds, composition, a method of use, and the first recited process of making of compounds of Formula of claim 1 representing various substituents as Morpholine, Thiomorpholine, Pyrazine (which constitute compounds/structures falling in class 544), on the piperazine core, and applicants have also elected species of working example compound 73-(2) as recited on page 151 of the specification, which is (2R)-1-(3,5-BIS(trifluoromethyl)benzoyl)-4-(4-(S)-3-ethylmorpholino)-2-butynyl)-2-((1H-indol-3-yl)methyl)piperazine dihydrochloride.

The elected species was not found in the prior art. When the search was expanded to compounds of Formula of claim 1 for the variables R1, Y, R2, R3, R4 then art was found.

**(2). Rejections maintained:** Applicants' arguments, remarks and admission of prior art(s) are considered but not found persuasive for withdrawal of rejections made under 35 U.S.C. 112 paragraph one for claims 1-6,8.(see also rejections under 35 U.S.C. 102/103(a) below).

**(3). New rejections:**

***Claim Rejections - 35 U.S.C. § 102***

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless -

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-6,8 (readable on Formula of claim 1) are rejected under 35 U.S.C. 102(b) as being anticipated by Matsuo et al(WO 9637489). The instantly claimed compounds read on the compounds of the reference, see claims 1,8 and compounds having CAS RN #169458-43-9 (= Piperazine,1-(3,5-BIS(trifluoromethyl)benzoyl)-2-(1H-indol-3-ylmethyl)-4(phenyl methyl)-); CAS RN # 169459-22-7(= Piperazine, 1-(3,5-BIS(trifluoromethyl)benzoyl)-2-(phenyl methyl)-4-(3-pyridinylmethyl)-dihydrochloride; CAS RN # 169460-36-0(= 1-piperazine acetic acid, 4-(3,5-BIS(trifluoromethyl)benzoyl)-3-(1H-indol-3-ylmethyl)-,phenyl methyl ester); CAS RN # 169461-19-2 ( = Unesterified compound of CAS RN 16960-36-0).

Claims 1-6,8 are rejected under 35 U.S.C. 102(b) as being anticipated by Anthony Neville J. Et al( WO 9630343 also cited as Chem Abstract 126:8133) The instantly claimed compounds read on the compounds of reference, see the compound having CAS RN # 183498-91-1/183498-92-2(= Piperazine,1-(1H-imidazole-4-ylmethyl)-4-(1-naphthalenylcarbonyl)-2-(phenyl methyl)-/BIS trifluoroacetate salt).

Claims 1-6,8 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsuo, Masaki et al (EP 655442). The instantly claimed compounds and claims 1-3,5-6,8 read on the compounds of reference, see the Formulae of abstract on page 1; compounds 50-44, 50-48 in Table 1 on pages 71,73; compounds of Table 2 in pages 82-84; Example 55 on page 91, Example 60 and species of Table 11 on pages 100-102, and claim 1 on page 106).

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Claims 1-6,8 are rejected under 35 U.S.C. 102(b) as being anticipated by Shue et al(WO 9708166). The instantly claimed compounds and claims 1,6 read on the compounds of reference, see the Formulae of abstract on page 1 and compounds of claim 1 on page 94).

Claims 1-6,8 are rejected under 35 U.S.C. 102(b) as being anticipated by Shue et al(WO 9634864). The instantly claimed compounds and claims 1,2,6 read on the compounds of reference, see the Formulae of abstract on page 1 and compounds of Example 6 on page 65, Example 14 on page 71, and claim 1 on page 108).

### ***Claim Rejections - 35 U.S.C. § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6,8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuo et al(WO 9637489).

The applicants claim generically substituted 1,4-diazine derivatives of Formula of claim 1 wherein R1 = aryl; R2 = aryl or indoyl; R3 = H or lower alkyl; R4 = substituted Non-heterocycles or Heterocycles or linear aliphatic compounds providing a variety of compounds.

The ref. '489 teaches making of saturated bridge/chains(see compounds of claim 1 on page 38 and compounds of claim 8 on page 42)as claimed herein in claims 1,5,6. Additionally, ref.'489 also teaches the pharmaceutical use of such compounds(see pages 1-2).

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One of ordinary skill in the art would have been motivated to select the claimed compounds from the reference genus since such compounds would have been suggested by the reference as a whole.

Compounds Claim 8 of ref. '489 differ from the instant application by reciting more broader genus, however it would have been obvious to a chemist skilled in the art to select any species of the genus that will have reasonably similar properties and equal or better pharmaceutical use. One of ordinary skill in the art would have been motivated to select the claimed compounds from the reference genus and make it by process claim 3(see page 39) since such compounds would have been suggested by the reference as a whole. The requisite motivation stems from the expectation that compounds so structurally similar would be expected to possess pharmaceutical properties(in re Wood, 199 USPQ 137).

Claims 1-6,8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shue et al(WO 9634864). The ref. Shue et al teaches piperazino derivatives as neurokinin antagonists as taught herein(see Examples 6 on page 65; Example 14 on page 71; compounds of claim 1 on page 108; composition claim 22 on page 130; and method of use claim 23 on pages 130-131). The instantly claims compounds differ by having unsaturation in bridge/chain linking with R4 component. One of ordinary skill in art would have been motivated to make compounds similar to instant claims 1,2,6 by varying the variables Ar1(phenyl or naphthyl), Ar2(= heteroary or phenyl or naphthyl) and the substituents on to these rings. The requisite motivation stems from

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the expectation of success for compounds having 1,4-piperazine core of prior art(s) teaching pharmacological activity related to neurokinin antagonists.

Claims 1-6,8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuo et al(EP 655442). The ref.'442 teaches piperazino derivatives as Tachykinin antagonists as taught herein(see the Formulae of abstract on page 1; compounds 50-44, 50-48 in Table 1 on pages 71,73; compounds of Table 2 in pages 82-84; Example 55 on page 91, Example 60 and species of Table 11 on pages 100-102, and claim 1 on page 106).The instantly claimed compounds differ by having varying unsaturation in bridge/chain of R4 component. One of ordinary skill in art would have been motivated to make compounds similar to instant claims 1-3,5-6 by varying the variables -A-(Z)p wherein Z = heterocyclic ring. The requisite motivation stems from the expectation of success for compounds having 1,4-piperazine core of prior art(s) teaching pharmacological activity related to Tachykinin antagonists.

Claims 1-6,8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shue et al(WO 9708166). The ref.'166 teaches piperazino derivatives as Neurokinin antagonists as taught herein(see the Formulae of abstract on page 1 and compounds of claim 1 on page 94). The instantly claimed compounds differ by having varying unsaturation in bridge/chain of R4 component. One of ordinary skill in art would have been motivated to make compounds similar to instant claims 1,6 by varying the variables Ar1, Ar2(= heterocyclic ring). The requisite motivation stems from the expectation of success for compounds having 1,4-piperazine core of prior art(s) teaching pharmacological activity related to Neurokinin antagonists.

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Claims 6,8 are rejected under 35 U.S.C. 103(a) over Matsuo et al(EP 655442 see page 3 lines 2-20 and composition claim 7 on page 113) which teach the use of Tachykinin antagonists for treating Tachykinin-mediated disease for example in treatment of respiratory disease such as asthma. Also see applicants admission in page 2 lines 9-11 of the specification.

**(4). References:**

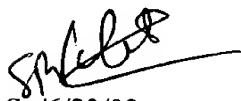
The references cited in the International Search report dated 11/11/98 have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO-1449 or PTO/SB/08A and 08B form, must be filed within the set period for reply to this Office Action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel, D.Sc.Tech. whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr.Mukund Shah can be reached at (703) 308 4716 or Sr. Examiner Mr. Richard Raymond at (730) 308 4523.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

  
Sp/6/23/02.

  
MUKUND J. SHAH  
SUPERVISORY PATENT EXAMINER  
GROUP 1600